

We claim:

1. A peptide compound of the formula [I] [SEQ. ID. NO. 4]:

Xaa₁ Xaa₂ Xaa₃ Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀
Xaa₁₁ Xaa₁₂ Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀
Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅ Xaa₂₆ Xaa₂₇ Xaa₂₈-Z₁; wherein

Xaa₁ is His, Arg, Tyr, Ala, Norval, Val
or Norleu;

Xaa₂ is Ser, Gly, Ala or Thr;

Xaa₃ is Ala, Asp or Glu;

Xaa₄ is Ala, Norval, Val, Norleu or Gly;

Xaa₅ is Ala or Thr;

Xaa₆ is Phe, Tyr or naphthylalanine;

Xaa₇ is Thr or Ser;

Xaa₈ is Ala, Ser or Thr;

Xaa₉ is Ala, Norval, Val, Norleu, Asp or Glu;

Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;

Xaa₁₁ is Ala or Ser;

Xaa₁₂ is Ala or Lys;

Xaa₁₃ is Ala or Gln;

Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;

Xaa₁₅ is Ala or Glu;

Xaa₁₆ is Ala or Glu;

Xaa₁₇ is Ala or Glu;

Xaa₁₉ is Ala or Val;

Xaa₂₀ is Ala or Arg;

Xaa₂₁ is Ala or Leu;
 Xaa₂₂ is Phe, Tyr or naphthylalanine;
 Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
 Xaa₂₄ is Ala, Glu or Asp;
 Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;
 Xaa₂₆ is Ala or Leu;
 Xaa₂₇ is Ala or Lys;
 Xaa₂₈ is Ala or Asn;
 Z₁ is -OH,

-NH₂,

Gly-Z₂,

Gly Gly-Z₂

Gly Gly Xaa₃₁-Z₂,

Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Xaa₃₉-Z₂;

wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently
 selected from the group consisting of Pro,
 homoproline, 3Hyp, 4Hyp, thioproline,
 N-alkylglycine, N-alkylpentylglycine and
 N-alkylalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈,
 Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉,

Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₂₈ are Ala; and provided also that, if Xaa₁ is His, Arg or Tyr, then at least one of Xaa₃, Xaa₄ and Xaa₉ is Ala; and pharmaceutically acceptable salts thereof;

2. A compound according to claim 1 wherein Xaa₁ is His, Ala or Norval.

3. A compound according to claim 1 wherein Xaa₁ is Ala.

4. A compound according to claim 2 wherein Xaa₁ is Ala.

5. A compound according to claim 1 wherein Xaa₁ is His.

6. A compound according to claim 2 wherein Xaa₁ is His.

7. A compound according to claim 1 wherein Xaa₂ is Gly.

8. A compound according to claim 2 wherein Xaa₂ is Gly.

9. A compound according to claim 1 wherein Xaa₃ is Ala.

10. A compound according to claim 2 where Xaa₃ is Ala.

11. A compound according to claim 1 wherein Xaa₄ is Ala.

12. A compound according to claim 2 where Xaa₄ is Ala.

13. A compound according to claim 1 wherein Xaa₉ is Ala.

14. A compound according to claim 2 where Xaa₉ is Ala.
15. A compound according to any of claims 8-14 wherein Xaa₁₄ is Leu, pentyglycine or Met.
16. A compound according to claim 15 wherein Xaa₂₅ is Trp or Phe.
17. A compound according to claim 16 wherein Xaa₆ is Ala, Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.
18. A compound according to claim 17 wherein Z₁ is -NH₂.
19. A compound according to claim 17 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
20. A compound according to claim 1 wherein Xaa₃₉ is Ser or Tyr.
21. A compound according to claim 17 wherein Xaa₃₉ is Ser or Tyr.
22. A compound according to claim 1 wherein Xaa₃₉ is Ser.
23. A compound according to claim 17 wherein Xaa₃₉ is Ser.

24. A compound according to claim 1 wherein Z_2 is $-NH_2$.

25. A compound according to any of claims 19, 21 or 23 wherein Z_2 is $-NH_2$.

26. A compound according to claim 1 wherein Z_1 is $-NH_2$.

27. A compound according to claim 1 wherein Xaa_{31} , Xaa_{36} , Xaa_{37} and Xaa_{38} are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

28. A compound according to claim 1 which has an amino acid sequence selected from SEQ. ID. NOS. 5 to 93.

29. A peptide compound of the formula [I] [SEQ. ID. NO. 4]:

$Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13}$
 $Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{18} Xaa_{19} Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25}$
 $Xaa_{26} Xaa_{27} Xaa_{28}-Z_1$; wherein

Xaa_1 is His or Ala;

Xaa_2 is Gly or Ala;

Xaa_3 is Ala, Asp or Glu;

Xaa_4 is Ala or Gly;

Xaa_5 is Ala or Thr;

Xaa_6 is Phe or naphthylalanine;

Xaa_7 is Thr or Ser;

Xaa_8 is Ala, Ser or Thr;

Xaa₉ is Ala, Asp or Glu;
 Xaa₁₀ is Ala, Leu or pentylglycine;
 Xaa₁₁ is Ala or Ser;
 Xaa₁₂ is Ala or Lys;
 Xaa₁₃ is Ala or Gln;
 Xaa₁₄ is Ala, Leu, Met or pentylglycine;
 Xaa₁₅ is Ala or Glu;
 Xaa₁₆ is Ala or Glu;
 Xaa₁₇ is Ala or Glu;
 Xaa₁₉ is Ala or Val;
 Xaa₂₀ is Ala or Arg;
 Xaa₂₁ is Ala or Leu;
 Xaa₂₂ is Phe or naphthylalanine;
 Xaa₂₃ is Ile, Val or tert-butylglycine;
 Xaa₂₄ is Ala, Glu or Asp;
 Xaa₂₅ is Ala, Trp or Phe;
 Xaa₂₆ is Ala or Leu;
 Xaa₂₇ is Ala or Lys;
 Xaa₂₈ is Ala or Asn;
 Z₁ is -OH,
 -NH₂,
 Gly-Z₂,
 Gly Gly-Z₂
 Gly Gly Xaa₃₁-Z₂,
 Gly Gly Xaa₃₁ Ser-Z₂,
 Gly Gly Xaa₃₁ Ser Ser-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈
Ser-Z₂;

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently Pro,
homoproline, thioproline, or
N-methylalalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₅, Xaa₆, Xaa₈, Xaa₁₀,
Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁,
Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₂₈ are Ala; and provided that, if
Xaa₁ is His, Arg or Tyr, then at least one of Xaa₃, Xaa₄ and Xaa₉
is Ala; and pharmaceutically acceptable salts thereof;

30. A compound according to claim 29 which has an amino
acid sequence selected from SEQ. ID. NOS. 5-9.

31. A composition comprising a compound of any of claims 1
to 29 in a pharmaceutically acceptable carrier.

32. A composition comprising a compound of claim 30 in a
pharmaceutically acceptable carrier.

33. A method for the treatment of diabetes mellitus
comprising the administration of a therapeutically effective
amount of a compound according to claim 1.

34. A method for the treatment of diabetes mellitus
comprising the administration of a therapeutically effective
amount of a compound according to claim 28.

35. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 29.

36. The method of claim 33 further comprising the administration of a therapeutically effective amount of an insulin.

37. The method of claim 34 further comprising the administration of a therapeutically effective amount of an insulin.

38. The method of claim 35 further comprising the administration of a therapeutically effective amount of an insulin.

39. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 1.

40. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 28.

41. A method for the treatment of a hypoglycemic condition in a mammal comprising the step of administering a

therapeutically effective amount of a compound according to claim 29.

42. A peptide compound of the formula (II) [SEQ. ID. NO. 94]:

5 10

Xaa₁ Xaa₂ Xaa₃ Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀

Xaa₁₁ Xaa₁₂ Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀

Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅ Xaa₂₆ X_{1-Z₁}; wherein

Xaa₁ is His, Arg, Tyr, Ala, Norval, Val, Norleu or 4-imidazopropionyl;

Xaa₂ is Ser, Gly, Ala or Thr;

Xaa₃ is Ala, Asp or Glu;

Xaa₄ is Ala, Norval, Val, Norleu or Gly;

Xaa₅ is Ala or Thr;

Xaa₆ is Phe, Tyr or naphthylalanine;

Xaa₇ is Thr or Ser;

Xaa₈ is Ala, Ser or Thr;

Xaa₉ is Ala, Norval, Val, Norleu, Asp or Glu;

Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;

Xaa₁₁ is Ala or Ser;

Xaa₁₂ is Ala or Lys;

Xaa₁₃ is Ala or Gln;

Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;

Xaa₁₅ is Ala or Glu;

Xaa₁₆ is Ala or Glu;

Xaa₁₇ is Ala or Glu;

Xaa₁₉ is Ala or Val;

Xaa₂₀ is Ala or Arg;

Xaa₂₁ is Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkyl alkanoyl Ala, Leu or;

Xaa₂₂ is Phe, Tyr or naphthylalanine;

Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;

Xaa₂₄ is Ala, Glu or Asp;

Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa₂₆ is Ala or Leu;

X₁ is Lys Asn, Asn Lys, Lys-NH^e-R Asn, Asn Lys-NH^e-R, Lys-NH^e-R Ala, Ala Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylalkanoyl

Z₁ is -OH,

-NH₂,

Gly-Z₂,

Gly Gly-Z₂,

Gly Gly Xaa₃₁-Z₂,

Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Xaa₃₉-Z₂;

wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine and N-alkylalanine; and

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Z_2 is -OH or -NH₂.

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, are Ala; and provided also that, if Xaa₁ is His, Arg, Tyr, or 4-imidazopropionyl then at least one of Xaa₃, Xaa₄ and Xaa₉ is Ala; and pharmaceutically acceptable salts thereof.

43. A compound according to claim 42 wherein Xaa₁ is His, Ala, Norval or 4-imidazopropionyl.

44. A compound according to claim 43 wherein Xaa₁ is His or 4-imidazopropionyl.

45. A compound according to claim 43 wherein Xaa₁ is Ala.

46. A compound according to claim 43 wherein Xaa₁ is His.

47. A compound according to claim 43 wherein Xaa₁ is 4-imidazopropionyl.

48. A compound according to claim 42 wherein Xaa₂ is Gly.

49. A compound according to any of claims 43-47 wherein Xaa₂ is Gly.

50. A compound according to claim 42 wherein Xaa₃ is Ala.

51. A compound according to any of claims 43-47 where Xaa₃ is Ala.

52. A compound according to claim 42 wherein Xaa₄ is Ala.
53. A compound according to any of claims 43-47 where Xaa₄ is Ala.
54. A compound according to claim 42 wherein Xaa₉ is Ala.
55. A compound according to any of claim 43-47 where Xaa₉ is Ala.
56. A compound according to claim 42 wherein Xaa₁₄ is Leu, pentylglycine or Met.
57. A compound according to claim 42 wherein Xaa₂₅ is Trp or Phe.
58. A compound according to claim 42 wherein Xaa₆ is Ala, Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.
59. A compound according to claim 42 wherein Z₁ is -NH₂.
60. A compound according to claim 42 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
61. A compound according to claim 42 wherein Xaa₃₉ is Ser or Tyr.

62. A compound according to claim 58 wherein Xaa₃₉ is Ser or Tyr.

63. A compound according to claim 42 wherein Xaa₃₉ is Ser.

64. A compound according to claim 58 wherein Xaa₃₉ is Ser.

65. A compound according to claim 42 wherein Z₂ is -NH₂.

66. A compound according to any of claims 50, 52 or 54 wherein Z₂ is -NH₂.

67. A compound according to claim 42 wherein Z₁ is -NH₂.

68. A compound according to claim 42 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

69. A compound according to claim 42 wherein X₁ is Lys Asn, Lys-NH^e-R Asn, or Lys-NH^e-R Ala where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

70. A compound according to claim 42 wherein Xaa₂₁ is Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkyl-alkanoyl

(1) The first part of the paper is devoted to the study of the asymptotic behavior of the solutions of the system (1.1) as $t \rightarrow \infty$. It is shown that the solutions of the system (1.1) are bounded and tend to zero as $t \rightarrow \infty$.